flamed, sealed and incubated for a minimum of 6 days at 37.5°C. This method provides partial anærobic conditions and has been found to enhance the growth of organisms of a partially anærobic nature.

This case was characterized by:— (1) a daily pyrexia, the rise beginning at 4 p.m., reaching its maximum at 8 p.m., with a pulse not proportional to the degree of temperature; (2) an enlarged, tender, and palpable spleen; (3) migratory joint pains simulating acute rheumatic fever; (4) secondary anæmia; (5) positive agglutinations against *Br. abortus*, beginning at titres of 1:10 and reaching 1:1,600; (6) the isolation of the organism from the blood stream on several occasions.

Our thanks are due Drs. R. S. Stevens and T. R. Little for their kindly assistance in this case.

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Editorial

THROMBOCYTOPENIA AS A MANIFESTATION OF POISONING

THE occurrence of purpura, cured permanently, or relieved for more or less prolonged periods, by splenectomy or tying the splenic artery, is always an arresting phenomenon, one which invites investigation and speculation. In these cases the essential feature is a diminution in the number of the blood platelets (thrombocytopenia) to a point somewhere below the lower norm of 30,000 per cubic millimetre. The operation of splenectomy is followed by a rapid and striking increase in the number of the platelets and the hæmorrhage stops. Kaznelson,[1] who was the first to try this procedure, was of the opinion that the deficiency in the circulating platelets was due to an abnormally active destruction of the platelets in the spleen, as he found large masses of platelets in a state of disintegration in that organ. While this observation has been confirmed in some cases it has not been substantiated in by far the majority. There is more evidence to support the opposing view of Frank, that the essential cause lies in a faulty development of the megacaryocytes in the bone marrow. How the operation of splenectomy produces such beneficial results is quite a puzzle. Waugh[2] believes that the changes following splenectomy are not specific for thrombocytopenia, in as much as they occur also after the removal of the normal organ in conditions other than that in question. He says, "Personally, I now look upon the beneficial effects of splenectomy in this condition (thrombocytopenic purpura, Ed.) as due to quite independent changes, which, fortunately, tend to correct the abnormalities which are present but in no way strike at the root of the disease. Moreover, while one cannot deny the histological abnormality of the megacaryocytes, the rapid production of platelets following excision of the spleen precludes any conception of more than a very simple injury or, perhaps better, inhibition."

It is well to point out, however, in considering this matter, that there are two main groups of thrombocytopenias:—(1) primary, idiopathic, or essential thrombocytopenia, of which Werlhof's disease is the most outstanding example; and (2) secondary or symptomatic thrombocytopenia. In the first no definite cause can be incriminated; in the second the causes are many and various, but have this in common that they all act deleteriously on the bone marrow. Perhaps the latter may be divided into three categories: (*a*) toxins, this term being used in a wide sense, (*b*) primary blood diseases, and (*c*) conditions in which the bone marrow is destroyed and replaced by other tissues. The toxic causes are exemplified occasionally in the course of certain of the acute infectious diseases, such as, scarlatina, measles, smallpox, diphtheria, typhoid fever, typhus, cerebrospinal fever and sepsis; in chemical

1. KAZNELSON, P., *Wien. Arch. f. inn. Med.*, 1923, **7**: 87.
2. WAUGH, T. R., The Classification of the Hæmorrhagic Diatheses, *Canad. Med. Ass. J.*, 1931, **25**: 331.

poisonings, as from arsenicals, bismuth, iodine, gold and benzene, which according to the degree of severity and specific action on the marrow are manifested as agranulocytosis, aleukia hæmorrhagica, aplastic anæmia and panmyelotoxicosis. The primary blood diseases that come into thought are Addisonian anæmia and the leukoses. The conditions which may cause replacement of the bone marrow are such things as carcinoma, lymphogranulomatosis, Gaucher's disease, Neuman-Pick disease, and osteosclerosis. It may properly be emphasized that before any procedure so drastic as removal of the spleen is undertaken in any given case of thrombocytopenia it should first be determined into which of the two groups the case falls. Every effort should be made to establish a cause, which, naturally, should be removed if possible. If no extrinsic cause can be ascertained splenectomy should be considered; then, and only then. If decided upon, the operation should be preceded by blood transfusion.

Much attention has been given of late to the subject of the harmful action of such drugs as amidopyrine, members of the barbituric acid series, dinitrophenol, and their congeners. Cases of fatal poisoning have been recorded which have been attributed to one or more of these agents. In some the clinical picture known as agranulocytosis or granulocytopenia has been manifested, and much evidence has been accumulated to show that this is due to the action of the common benzene radicle on the bone marrow.

Similarly, purpura, with thrombocytopenia, has been noted following the employment of certain other of the new hypnotics. Thus, Morawitz[3] records the occurrence of "purpura Majochi", polycythæmia, and, later, slight thrombocytopenia after the use of acetyladalin, and Jones and Jacobs[4] had a case in which the use of nirvanol was followed by severe thrombocytopenic purpura. Again, in a quite recent communication, Dr. F. E. Loewy[5] reports the occurrence of a typical case of Werlhof's disease and two milder cases of thrombocytopenic purpura which were due to the prolonged administration of a well-known hypnotic, "sedormid," in hypersensitive patients. "Sedormid" is allyl-iso-propyl-acetyl-urea. The first patient, a man aged sixty-one, had been taking sedormid in doses of four to eight grains frequently during the preceding three years. His illness was characterized by the appearance of purpura, ecchymoses, severe bleeding from the gums after the extraction of a tooth, hæmaturia and melæna. The bleeding time was prolonged over many hours and the blood platelets numbered 22,000 per cubic millimetre. A transfusion of 600 c.c. of citrated blood produced marked improvement, and two days later the platelets were 120,000. The administration of eight grains of sedormid on three successive nights brought on thrombocytopenia again. The condition improved when the sedormid was omitted, and six days later the platelet count was 360,000. As an experiment, four grains of the drug were then administered, with the result that purpura reappeared and the platelets were reduced to very few (in one smear). In a week the count was normal again. Ten days afterwards a second test was made. Two grains of sedormid produced another attack of purpura in which the platelets were reduced to 17,000. Two weeks later the platelets numbered 347,000. "The case against sedormid was proved."

The second patient, a woman of sixty, had taken with good effect sedormid in doses of two to eight grains nightly for several weeks rather more than a year previously. For five and a half weeks before being seen by Dr. Loewy she had again taken 4 to 8 grains of sedormid nightly. One week after resuming the medication she developed purpura, extravasations of blood, retinal hæmorrhages, arthritic pains, and headache. Her bleeding time was markedly prolonged (over eight minutes), the tourniquet test was positive, and the platelets numbered 28,000. The sedormid was stopped, improvement set in, and a week later the bleeding time was normal and the number of the platelets was normal.

The third patient was a woman, aged fifty-one, who complained of bleeding from the gums which had come on a few hours after a sedormid tablet had been taken. Numerous purpuric spots were also present on the trunk and legs, but at the time of

3. MORAWITZ, P., *Deutsche med. Wchnschr.*, 1932, **58**: 375.
4. JONES, T. D. and JACOBS, J. L., *J. Am. M. Ass.*, 1932, **99**: 18.
5. LOEWY, F. E., *The Lancet*, 1934, **1**: 845.

examination she was somewhat improved. The bleeding time was normal, the tourniquet test negative, and the platelets were 36,000 per c.mm. This patient had taken sedormid in doses of two to four grains repeatedly during the previous year and had had during that time several attacks of purpura, and, once, a small retinal hæmorrhage. When the sedormid was stopped no further hæmorrhages occurred.

In commenting on these cases, Dr. Loewy remarks that in regard to the harmful effect produced by the prolonged administration of drugs it is necessary to distinguish (1) a direct toxic effect due to overdose or accumulation characteristic and specific for each drug; (2) a purely allergic effect, identical, *e.g.*, with serum sickness; and (3) an allergotoxic effect, where an over-dose can be excluded and the peculiar effects must be attributed to a gradual sensitization of the patient. He explains his cases on the last assumption. He concludes that "the modern hypnotics and sedatives are certainly valuable but never absolutely harmless, and careful supervision is required, especially with newly introduced drugs and hypersensitive patients with irritability of the digestive tract."

It is quite evident that the two most popular groups of sedatives, the barbituric acid series and the ureids (acetyl-adalin; sedormid), are competent, on occasion, to give rise to serious toxic disturbances, which may even threaten life. In both cases marked changes in the constitution of the blood are to be found; in the first, granulocytopenia, in the second, thrombocytopenia. In both cases skin rashes may appear; in the first, of urticarial type, in the second, purpura. While this is a generalization that may be admitted, it should be noted that one of the barbituric acid series (nirvanol) has been found to cause purpura. There may, therefore, be a common meeting ground. In the study of cases of granulocytopenia and thrombocytopenia investigation of the number and quality of the blood platelets should always be undertaken, for, by so doing, the relationship, if any, between the two conditions will be made clearer. In the recent literature on granulocytopenia this matter seems to have been overlooked. In determining the part played by the benzene radicle, which is at present under suspicion as the common toxic agent in causing certain of the cases of granulocytopenia, the point is of some importance. The benzene radicle is present in the barbituric acid groups, but is absent in the ureids. A.G.N.

CHANCE AND THE BLOOD COUNT

"SUPPOSE we have a patient suspected of acute appendicitis, whose differential count of 100 cells shows 70 per cent of polymorphonuclears, and an hour later, 80 per cent. Is this a significant change, or may it be due entirely to chance variation?" These sentences are quoted from a recent article by Barnett[1] on "The Unavoidable Error in the Differential Count of the Leukocytes of the Blood". It is a curious fact that, at this stage in the history of blood counting, an article of that kind should still be required in order to explain to laboratory workers and clinicians how to make allowance for the "chance" errors in the differential count.

If two differential counts are made on the blood of the same person at different times, everyone recognizes that the difference between the counts may be due to: (*a*) actual differences, physiological or pathological, in the person's blood; (*b*) differences in the observer or his technique. It does not seem, however, to be so clearly realized that a difference between the two counts should be expected even if the blood had exactly the same proportions of cells on the two occasions, and even if the technique and the observer's reactions were perfect. An argument by analogy may elucidate the point. Let it be supposed that many thousands of coins are tossed on to the floor and then picked up two at a time, purely at random, that is, without being previously looked at and so as not to give special preference either to those with head uppermost or to those with tail uppermost. If there is on the floor an exactly equal number with head up and with tail up, an average sample of two coins will

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